Studies on the Toxicity of Phthalates via Ingestion

by L. G. Krauskopf*

Introduction

Some recent publications have revealed the presence of phthalates in rather unexpected locations *(1—4)*. Mayer *(3)* reported that di-*n*-butyl phthalate and di-2-ethylhexyl phthalate had measurable effects on the *Daphnia*, an accepted subject for studying the aquatic food chain in the environment. The ubiquity of phthalates has been well documented. Their presence in stored blood samples and in some randomly sampled humans is reason for concern, even though no directly related harmful effect has been clearly demonstrated to date. Numerous nontechnical writings displayed serious concern about the subject of phthalates in the environment. Some of these writings showed signs of emotional reaction, inappropriate generalizations and an unawareness of the content of technical studies in the literature concerning the subject. Nearly one billion pounds of phthalates are consumed in the U.S.A. per year. They are a critically necessary component of plastics, coatings and other industries that are an integral part of our life.

In order to encourage mature perspective concerning the presence and effects of phthalates in our environment, one must retain perspective concerning the relative hazard or safety of various substances as a function of specific conditions involved. One accepted means for judging toxic characteristics of substances is to observe the effects due to oral ingestion. This report reviews published and unpublished studies on the oral ingestion of phthalates. The phthalates are compared to other known substances in terms of LD_{50} and acceptable daily intake (ADI) values.

*Research and Development Department, Union Carbide Corporation, Tarrytown Technical Center, Tarrytown, New York 10591.

Discussion

The literature reports ingestion studies on phthalates ranging from dimethyl (CH_3) up to ditridecyl ($C_{13}H_{27}$) and includes coesters of mixed alkyl alcohols as well as aryl alkyl phthalates. Dibutyl phthalates and di-2-ethylhexyl phthalate were appropriately the most widely studied, since they are the most significant members of the phthalate family from the viewpoint of volume consumed. Test animals covered a wide range, with the rat being the most common species. Other variables included the method of administration, i.e., stomach tube, capsules, added to diet, etc. Single-dose, acute-toxicity studies were generally employed for purposes of the statistically calculated LD_{50}, the dosage required to cause fatality to 50% of the test species. Prolonged ingestion studies generally involved daily dosages well below the LD_{50} values. Di-2-ethylhexyl phthalate (commonly referred to as DOP) was administered to various species up to 2 years *(5, 6)*. Harris et al. *(6)* pointed out that the natural lifetime of the control rats not receiving test sub-

stances precluded extending the exposure period past 2 years. Lefaux *(7)* reports that extensive feeding tests were conducted on rats with dibutyl phthalate at Villejuif Cancer Institute. Five generations of rats were fed daily diets containing 100 mg of DBP per kilogram body weight; 300 mg/kg and 500 mg/kg daily doses were fed to three generations of rats. Both male and female rats showed normal weight gains and reproductive patterns. No signs of poisoning or carcinogenic effects were found. It was concluded that dibutyl phthalate is harmless. Similarly, diets containing 500 mg of DOP/kg of body weight were fed to four generations of rats. Normal reproduction and no anomalies were found during parturition or nursing.

Tables 1–4 summarize the technical information contained in the literature on the ingestion of phthalates and related materials. While lethal dosages were, of course, attained, all of the writers reached the general conclusion that the phthalates have a very low order of toxicity. No carcinogenic characteristics were found by any of the investigators. Generally, no adverse histological or pathological effects of significance were found. Most investigators observed a slight reduction in rate of weight gain, and a slight increase in liver and kidney weights with specimens receiving the larger doses over prolonged periods. However, Harris et al. *(6)* reported none of these shortcomings for rats receiving DOP at 0.5% of the daily diet for 2 yr. This daily dose corresponded to a dose per body weight value ranging from 1.5 g/kg/day to 0.33 g/kg/day over the 2-yr feeding period. In the same work, a dog was fed 5.0 g/kg/day over a 14-week period. The only effect on the dog was a slight loss in rate of weight gain. The work of Harris et al. *(6, 24)* constituted the largest daily doses administered to test animals over extended periods.

Three cases of human ingestion, single dose, have been reported. Shaffer et al. *(14)* reported that an adult male intentionally took 10 g of di-2-ethylhexyl phthalate and experienced mild diarrhea; another adult male showed no effects whatsoever after having taken 5 g. Lefaux *(7)* reports that a young adult male mistakenly ingested about 10 g. of dibutyl phthalate. He was hospitalized on the next day, after having experienced nausea and vertigo. Signs of keratitis and toxic nephritis (excess albumen in the urine, together with red and white corpuscles) were observed. He was treated and released after 2 weeks observation with no after-effects. If a typical weight of the cited three subjects of 70 kg (154 lb) is assumed, it may be calculated that the 5 and 10 g dosages are equivalent to 72 and 144 mg/kg body weight, respectively. Hence, if a typical adult were to ingest a single dose of 10 g of phthalate plasticizer, it would be about 1/100 to 1/1000 of the single-dose LD_{50} levels reported in Table 1.

No investigator proposes that the quantitative values defined on test animals can be related to man. Uncontrolled dosages and exposures further complicate the problem of defining the safe use of substances. For the sake of comparison, therefore, Table 5 lists the LD_{50}, in rats, of some commonly encountered substances. LD_{50} values of typical common household chemicals that are considered safe are as follows: vinegar (acetic acid), 3.5–5.2 g/kg; table salt (sodium chloride), 4.5 g/kg; rubbing alcohol (isopropanol, not denatured), 5.8–10.7 g/kg; drinking alcohol (ethanol, not denatured), 11.3–21.3 g/kg; soapy water (20%), > 16 g/kg. All LD_{50} values are calculated to reflect the dosage of the 100% pure substance causing fatality to 50% of the specimens *(9)*. The ranges shown reflect findings that when administered in a more dilute condition, the animal has a reduced tolerance for total intake of the pure substance. The relative safety of the phthalates is recognized when the above substances are compared to the data in Table 1. Other than dimethyl phthalate, all of the phthalates tested for oral ingestion are included within the range of 8 g/kg to > 64 g/kg, LD_{50}. Dimethyl phthalate is frequently applied as an insecticide and may be expected to be unique in this class of materials. Dibutyl phthalate is in the same gen-

Table 1. Acute oral toxicity of phthalates.

Phthalate	Species	LD_{50}	Reference
Symmetrical			
Dimethyl	Guinea pig	2.4 g/kg	*(8)*
	Mouse	7.2 g/kg	*(8)*
	Rabbit	4.4 g/kg	*(8)*
	Rat	6.9 g/kg	*(8)*
	Rat	6.7 g/kg	*(9)*
	Rat	6.8 g/kg	*(10)*
Diethyl	Rat	8.2 ml/kg	*(11)*
Dibutyl	Rat	>20 g/kg	*(8)*
	Rat	ca. 8 g/kg	*(12)*
	Rat	8–10 g/kg	*(7)*
	Rat	10 g/kg	*(7)*
Di-*n*-butyl	Rat	12.6 g/kg	*(13)*
Di-*n*-hexyl	Rat (males)	29.6 ml/kg	*(9)*
	Rat (females)	38.9 ml/kg	*(9)*
Dicyclohexyl	Rat	30 ml/kg	*(7)*
Diisooctyl	Rat	22.6 ml/kg	*(13)*
Di-2-ethylhexyl	Guinea pig	26.3 g/kg	*(9)*
	Mouse	34.0 ml/kg	*(9)*
	Rabbit	33.9 g/kg	*(14)*
	Rat	30.6 g/kg	*(14)*
	Rat	34.3 ml/kg	*(9)*
Diisononyl	Rat	>10 g/kg	*(15)*
Diisodecyl	Rat	>64 ml/kg	*(16)*
Ditridecyl	Rat	>64 ml/kg	*(16)*
Coesters of alcohol mixtures			
Butyl, octyl	Rat	>63 ml/kg	*(13)*
Butyl, decyl	Rat	20.8 ml/kg	*(17)*
Hexyl, decyl	Rat	49.4 ml/kg	*(17)*
n-Hexyl, *n*-octyl, *n*-decyl	Rat	45.2 ml/kg	*(13)*
Heptyl, nonyl	Mouse	>19.3 g/kg	*(18)*
	Rat	>19.3 g/kg	*(18)*
Heptyl, nonyl, undecyl	Mouse	>20 g/kg	*(18)*
	Rat	>20 g/kg	*(18)*
	Rat	>64 g/kg	*(13)*
Octyl, decyl	Rat	45.2 ml/kg	*(17)*
	Rat	>63 ml/kg	*(13)*
2-Ethylhexyl, benzyl	Rat	60.3 g/kg	*(19)*
Nonyl, undecyl	Mouse	>19.7 g/kg	*(18)*
	Rat	>19.7 g/kg	*(18)*
Related diesters			
Di-2-ethylhexyl tetrahydrophthalate	Rat	>114 ml/kg	*(13)*
Di-2-ethylhexyl hexahydrophthalate	Rat	>63 g/kg	*(13)*
Di-2-ethylhexyl isophthalate	Rat	17.3 ml/kg	*(16)*
Diisodecyl isophthalate	Rat	>64 ml/kg	*(16)*
Diisodecyl tetrahydro-4, 5-epoxyphthalate	Rat	>63 ml/kg	*(13)*

Table 1. Acute oral toxicity of phthalates (continued).

Phthalate	Species	LD_{50}	Reference
Plasticizer alcohols			
n-Butanol	Rat	4.36 g/kg	*(17)*
	Rat	0.93 ml/kg	*(16)*
Isobutanol	Rat	2.46 g/kg	*(20)*
2-Ethylbutanol	Rat	1.86 g/kg	*(20)*
2-Methylpentanol	Rat	1.41 g/kg	*(20)*
n-Hexanol	Rat	4.59 g/kg	*(21)*
2, 2, 4-Trimethylpentanol	Rat	3.73 ml/kg	*(16)*
2-Ethylhexanol	Rat	2.46 ml/kg	*(17)*
	Rat	0.8 ml/kg	*(22)*
Isodecanol	Rat	9.80 g/kg	(17)
Isotridecanol	Rat	17.2 ml/kg	*(16)*
o-Phthalic acid	Rat	7.9 ml/kg	*(14)*

eral toxicity range of the household substances cited above, but all of the higher molecular weight phthalates are significantly less toxic than these substances. Because of the very low order of toxicity for these higher phthalates, no pattern is apparent as a function of variations in chemical structure. Other diesters that are similar to the phthalates were found to have very low order of toxicity as shown in Table 1. Typical plasticizer alcohols and phthalic acid, however, appear to be more toxic than the phthalates. As shown in Table 1, these materials all have LD_{50} of less than 20 g/kg.

The Joint FAO/WHO Expert Committee on Food Additives *(32)* strongly recommends that food additives be restricted to the minimum levels required to accomplish a given technical objective. It would, of course, be most desirable to have no foreign substance present in foods, but it must be recognized that such substances do enter foods by both direct and indirect means. Acceptable daily intake zones—commonly referred to as ADI—have been determined for various substances, and are expressed as milligrams per kilogram of man body weight *(32)*. The ADI is determined by the equation:

$$\text{ADI (mg/kg)} = N/F$$

where N denotes the maximum "no effect" level of substance based on most sensitive test with most sensitive test species, in mg/kg/day. (This usually implies daily dosages of duration $\geqq$ 90 days), F is a safety factor to convert from animal species to man. FAO/WHO recommends *(33)* a factor of 100; commonly, a factor of 500 is used if N is based on 90-day feeding test data and a factor of 100 is used if N is based on 2-year feeding tests. The typical daily intake may be calculated for a given food additive and compared to the ADI. Table 6 takes the liberty of calculating ADI values for phthalates, wherever the cited reference provided the pertinent information. The values range from 0.04*(7)* to 8.0 mg/kg. From this it may be estimated that a typical adult of 60 kg weight could survive daily doses of phthalates ranging from 2.4 mg to 480 mg (0.48 g). For further comparison, Table 7 lists ADI values of selected chemical compounds commonly applied as food additives. The unconditional acceptable limits of these chemicals have ADI values of the same order of magnitude that has been calculated for the phthalates.

Table 2. Summary of ingestion studies with dibutyl phthalate.

Reference	Species	Dose	Period	Observations and conclusions
(23)	Rats	2.5 mg/kg/day	6 months	No effect; recommended maximum level of 2 mg/l. in reservoir due to toxicity; taste and odor threshold at 5 mg/l.
(7)	Rats	4 g/kg	Single dose	Zero died
		8 g/kg	Single dose	4/9 died LD_{50} = 8-10 g/kg
		16 g/kg	Single dose	6/6 died
(7)	Rats	0.01%/day	1 yr	No effect
		0.05%/day	1 yr	
		1.25%/day	1 yr	50% died in 1 week; no lesions observed
(7)	Rats	5 ml/kg[a]	Single dose	All lived LD_{50} = 10 ml/kg; rabbits and
		15 ml/kg[a]	Single dose	All died; dogs LD_{50} similar to rats
		0.5 ml/kg[b]	1 yr	Nothing abnormal
		1.0 ml/kg[b]	1 yr	
(7)	Rats	100 mg/kg/day for 5 generations, also some for 21 months		No carcinogenic or poisonous effects
		300 mg/kg/day for 3 generations, also some for 21 months		
		500 mg/kg/day for 3 generations, also some for 15 months		
(7)	Human	≈ 10 g (accident for laxative)	Single dose	Nausea, vertigo, hepatitis, and toxic nephritis; released after 14 days in hospital.
(12)	Rats	4 g/kg	Single dose	Deaths 0/3 (no lethal effects)
		8 g/kg	Single dose	4/9
		16 g/kg	Single dose	6/6
		32 g/kg	Single dose	6/6
(12)	Rats	0.25%[c]	1 yr	No effect[d]
		1.25%	1 yr	50% fatal in 1 week; other 50% similar to controls. No gross or microscopic changes; DBP metabolized by pancreatic lipases[d]

[a] Administered at 50% in olive oil.

[b] Administered at 50% solution, 2 times/week.

[c] 350-110/mg/kg body weight.

[d] Acute oral lethal dose = 8 g/kg.

Summary and Conclusions

Extensive testing has been reported concerning the effects of ingestion of phthalates. The literature contains studies including phthalates ranging from dimethyl to ditridecyl. Acute toxicity tests define rather high LD_{50} values, indicating a very low order of toxicity as compared to many common chemical substances. The acceptable daily intake (ADI) values calculated for phthalates from the works cited are in the same order of magnitude as some chemicals that are approved for use as direct food additives. Three instances of human ingestion were reported. In one of the cases (dibutyl), some toxic symptoms were reported, but the person recovered with no after-effects; the other cases (DOP) showed no toxic effects.

The various works did reach levels of administration causing toxic effects, including fatalities of some of the test species.

Nearly all of the investigators were willing to conclude that the phthalates constitute a chemical family of very low order of toxicity, as measured by ingestion methods. Dimethyl phthalate, the lowest molecular weight member of the family, is mildly more toxic than all of the other phthalates, but is not considered lethal.

The extensive feeding studies that have been reported appear to verify that the phthalates have a very low order of toxicity when administered by oral ingestion.

Table 3. Summary of ingestion studies with di-2-ethylhexyl phthalate.

Reference	Species	Dose	Period	Observation and conclusions
(13)	Rats	0.13% in diet	2 yr	No effect
	Dogs	0.13%	1 yr	No effect
(23)	Rats	0.5 mg/kg/day	6 mo	No effect; recommend maximum level of DOP tolerable in water (reservoir) is 2.5 mg/l. based on odor and taste.
(5)	32 Male rats[a]	0.4% of diet	2 yr	
	32 Female rats[a]	0.13%	2 yr	No effect; no-effect level >0.13, <0.4% (>0.06 g/kg/day, <0.29/kg/day)
		0.04%	2 yr	
		0.0%	2 yr	
	80 Filial rats[a]	0.4% of diet	1 yr	No effect
		0.0%	1 yr	
(5)	Guinea pigs (males and	0.0%	1 yr	No effect on liver and kidney weights of males and kidney weights of females, but liver weights of females were 13% > controls (unexplainable).
		0.4%	1 yr	
	females)	0.13%	1 yr	No effect up to and involving 0.13% DOP in diet of guinea pigs close to 0.06 g/kg/day.
(5)	8 Dogs (14–17 months old)	0.03 ml/kg/day, 4 wk	1 yr total	*No effect; approximate no-effect level* = 0.06 ml/kg/day
		0.06 ml/kg/day, 48 wk	1 yr total	
(5)	1 Dog	0.06 ml/kg/day	15 wk	
		0.09 ml/kg/day	34 wk	
(24)	43 Male rats	0.0% of diet	3 mo	Mortality: no effect due to DOP
	43 Female rats	0.1%	6 mo	Body weight: no effect due to DOP
		0.5%	12 mo	Food intake: no effect for first year; but *0.5% group ate only 75% of control* group during second year
			24 mo	0.4%, Carpenter's rats ≈ 0.2
				No effect g/kg/day = 200 mg/kg
				0.1% in rats for 2 years
				Organ weights: no difference, except for slight increase of liver and kidney with 0.5% diet
				Pathology: no effect
(24)	2 Dogs	5 g/kg/day, stomach tube	14 wk	Mild toxic changes at 14 weeks, 0.1 g/kg/day gave no effect at 14 weeks, but it is pointed out that Carpenter *(5)* had found 0.09 ml/kg/day to give toxic changes in liver and kidney after 1 year feeding. Not harmful in industry or food wraps.
		0.1 g/kg/day in diet	14 wk	

Table 3. Summary of ingestion studies with di-2-ethylhexyl phthalate (continued).

Reference	Species	Dose	Period	Observation and conclusions
(22)	Mice	34.5 g/kg	Single dose	No fatalities
(14)	Rats	79.5 g/kg	Single dose	Killed 8/10 rats
(14)	5 Rats (male, weighing 120 - 150 g)	3.0% (1.9 g/kg/day)	90 days	Slight slowing of weight gain
		1.5% (0.9 g/kg/day)	90 days	
		0.75 (0.4 g/kg/day)	90 days	
		0.375% (0.2 g/kg/day)	90 days	No effect
		0.0% (0 g/kg/day)	90 days	
(14)	2 Humans (adult males)	10 g	Single dose	Diarrhea Urinalyses gave 4.5% of the
		5 g	Single dose	No effect dose within 24 hr
(14)	2 Dogs	2 g/kg	Single dose	Urinalyses: 2.0-4.5% of dose in 3 days
(14)	5 Rabbits	2 g/kg	Single dose	Urinalyses for 3 days: recovered 26-65% of dose (average = 42%)
(25)	Rats	61 ml/kg	Single dose	0/10 no effect; DOP very low order of toxicity. 34 g/kg gave no deaths.
(22)	Rats	25 g/kg, tube	Single dose	No effect
		110 g/kg, tube	Single dose	Diarrhea[d]
(26)	Rats	15.8 g/kg	Single dose	Nonlethal
(13)	Rats	0		Weights of all organs and bone marrow measured; only liver and kidney weights showed slight gains at 3 and 6 months. No clear-cut evidence of toxic effects, but 6-month specimens indicated that changes in bladder of 20% of species may be due to diet.
		0.1% of diet	3 mo	
		0.5% of diet	6 mo	
(6)	Rats	0	3 mo	Control group had 44/46 fatality; 2 yr is maximum period useful for rats
		0.1% of diet	6 mo	
		0.5% of diet	12 mo	ΔWeight: all same; all organs: no change. Liver and kidney definitely not > controls. Lungs, brain, stomach, heart, spleen, testes, also weighed
			24 mo	
				Pathological: test animals similar to controls (aging changes)
(6)	Rats	6/ml/kg, tube	Single dose	10/10 survived >7 days
(6)	Dogs	0.1 g/kg/day(female)	14 wk	No effect: slight loss of weight gain. Hematology: normal; Histological: normal; Urinalyses: no effect (on female only). At 10 g/kg, the dog refused to eat for 2 days.
		5.0 g/kg/day (male)	14 wk	
		10.0 g/kg/day		

[a]Test started at 2 months age of rats.

[b]Equal to 0.05 - 0.08 g/kg/day.

[c]Equal to 0.3 - 0.4 g/kg/day.

[d]Reports DOP much less toxic than DCP *(22)*.

Table 4. Summary of ingestion studies with various phthalates.

Phthalate	Reference	Species	Dose	Period	Observation and conclusions
Dimethyl phthalate					
	(7)	Mice	1–4 g/kg	Single dose	No effect
	(7)	Dogs	0.7–1.4 g/kg	Single dose	No effect
Di (mixed heptyl, nonyl) phthalate					
	(27)	Rats and mice (fasted 18 hr)	0[a] 0.125%[a] 0.25%[a] 0.5%[a] 1.0%[a]	90 days	1% level gave growth retardation to males; slight anemia in all at 0.25%, 0.5, 1.0% of diet; At 0.5, 1.0% kidney and liver weights increased; definitely no effect at 0.125%
	(27)	Rats and mice (fasted 18 hr)	20 g/kg	Single dose, acute	Diarrhea
Santicizer 711 [di(linear C_7, C_9 C_{11} mixed alcohol) phthalate]					
	(26)	Rats	20 g/kg	Single dose	No effect; nontoxic
Diisononyl phthalate					
	(15)	Rats	10 g/kg 5 g/kg	Single dose Single dose	Oily fur Oily fur; no loss in weight gain rate; Symptoms gone after 7 days; LD_{50} >10 g/kg
	(15)	Rats (male and female)	0 mg/kg/day 50 mg/kg/day 150 mg/kg/day 500 mg/kg/day	13 wk 13 wk 13 wk 13 wk	 No effect Liver weight increased; slight loss in body weight gain rates
	(15) 4	Dogs (male and female)	0% of diet 0.125%[b] 0.500% 2.0% 4.0%	13 wk 13 wk 13 wk 2% for 8 wk increased to 4% for 9–13 wk	 No effect Questionable no effect (weight gain of liver) Increase in liver weight; loss in body weight; histologic changes in liver, gall bladder, spleen, and kidney
Diisodecyl phthalate					
	(28)	Rats	30 ml/kg	Single dose	All survived
	(28)	Rabbits	30 ml/kg	Single dose	Minimum lethal dose calculated at 22.5–30 ml/kg
Diundecyl phthalate					
	(29)	Rats	15.8 g/kg	Single dose	Nonlethal; practically nontoxic
Dicyclohexyl phthalate					
	(7)	Rats	25% in olive oil 25% in olive oil	Single dose 7 days	None died at 24 hr; LD_{50} = 30 ml/kg; rabbits and dogs similar

Table 4. Summary of ingestion studies with various phthalates (continued).

Phthalate	Reference	Species	Dose	Period	Observation and conclusions
	(7)	Rats	0.5 ml/kg	2 doses/wk, 52 wk	No effects
			1.0 ml/kg	2 doses/wk, 52 wk	
	(7)	Rats	5 mg/kg 10 mg/kg 100 mg/kg	4 generations, also one for 18 mos	No effect, not carcinogenic
	(30)	Rats	31.2 g/kg (33% in water)	2 doses in 1 day	All survived
			62.4 g/kg (33% in water)	4 doses in 2 days	All survived
	(30)	Rabbits	23.0 g/kg	2 doses in 1 day	All survived
			44.1 g/kg	4 doses in 2 days	All survived; no phthalate was absorbed in intestinal tract by any rats or rabbits tested.
Butyl benzyl phthalate					
	(31)	Rats	0.25% of diet	90 days	No effect
			0.50%	90 days	
			1.00%	90 days	
			1.50%	90 days	Mild loss of growth rate
			2.00%	90 days	Mild loss of growth rate No adverse hematologic effects No effect in urinalysis Liver weight gain for 1.00, 1.5, 2.0% animals No histopathologic effects
	(31)	Dogs	1.0%, capsules[c]	90 days	No deaths. No effect on weight gain at 1.0 and 2.0%; 5.0% group gained less initially due to refusal to eat; capsules restored normal eating
			2.0% capsules[c]	90 days	
			5.0% capsules[c]	90 days	No effect found at all levels in hematological, urinalyses, liver and kidney functions All functioning parts at end of test

[a] 0, 0.125, 0.25, 0.5, 1.0% equivalent to 0, 0.05–0.16, 0.1–0.34, 0.21–0.66, and 0.45–1.33 g/kg/day, respectively.
[b] 0.125, 2.0, 4.0% equivalent to mean dose of 37,538, and 1340 (males) and 1075 (female) mg/kg/day, respectively.
[c] Wt-% of daily diet.

Table 5. Acute oral toxicity in rats of some common substances.[a]

Substance	Purity as administered, %	LD_{50}[b]	Reference
Acetic acid	100	5.2 ml/kg	*(9)*
	10, in water	3.5 g/kg	*(21)*
Boric acid	100	5.14 g/kg	*(17)*
Calcium hydroxide	100	7.34 g/kg	*(17)*

Table 5. Acute oral toxicity in rats of some common substances.[a] (continued)

Substance	Purity as administered, %	LD_{50}[b]	Reference
Calcium propionate	100	5.16 g/kg	*(17)*
Corn oil	100	>100 ml/kg	*(9)*
Ethanol	100	21.3 g/kg	*(9)*
	50, in water	13.6 g/kg	*(9)*
Fuel oil	100	15.4 ml/kg	*(9)*
Glycerine	100	27.5 g/kg	*(9)*
Isopropanol	100	10.7 ml/kg	*(9)*
	50, in water	8.7 ml/kg	*(9)*
	10, in water	5.8 ml/kg	*(9)*
Lard	100	>64 g/kg	*(9)*
Methanol	100	12.9 g/kg	*(9)*
Potassium acetate	100	3.25 g/kg	*(17)*
Soap (Ivory Snow)	20, in water	16 g/kg	*(17)*
Sodium chloride	10, in water	4.54 g/kg	*(17)*
Sorbic acid	10, in water	10.9 g/kg	*(17)*
Sucrose	50, in water	35.4 g/kg	*(17)*
Sulfuric acid	100	2.14 g/kg	*(17)*
Wine (commercial grade of 16% ethanol)	100	70.7 ml/kg[c]	*(9)*

[a] For method, see Smyth et al. *(16)*

[b] All values calculated on basis of 100% purity, irrespective of administration purity.

[c] 70.7 ml/kg wine equals 11.3 ml/kg ethanol content.

Table 6. ADI calculated from various investigations.

Phthalate	Species	Period, days	Maximum no-effect level, mg/kg/day	ADI, mg/kg[a]	Reference
Di-2-ethylhexyl	Rat	365	400	4.0	*(24)*
	Rat	730	80	8.0	*(24)*
	Dog	98	100	0.2	*(24)*
	Rat	90	200	0.4	*(14)*
	Dog	98	100	0.2	*(6)*
	Rat	365	>60, <200	>8.4, <28 >0.6, <2.0	*(5)*
	Guinea pig	365	ca. 60	ca. 0.6	*(5)*
	Dog	365	ca. 60	ca. 0.6	*(5)*
Dibutyl	Rat	365	350 - 110	3.5-1.1	*(12)*
	Rat	450	4.3	0.04	*(7)*

Table 6. ADI calculated from various investigations. (continued)

Phthalate	Species	Period, days	Maximum no-effect level, mg/kg/day	ADI, mg/kg[a]	Reference
Diisononyl	Rat	91	150	0.3	*(15)*
	Dog	91	37	0.07	*(15)*
Heptyl nonyl	Rat	90	ca. 60	ca. 0.12	*(27)*
	Mouse	90	ca. 60	ca. 0.12	*(27)*

[a]ADI = N/F, where F = 500 for $<$ 365 day period; 100 for $\geq$ 365 day period.

Table 7. Acceptable daily intakes for man of some antimicrobials, antioxidants, and antioxidant synergists.[a]

	Overall daily intake zone, mg/kg body weight[b]	
	Unconditional	Conditional
Benzoic acid Benzoate, potassium Benzoate, sodium	0 - 5[c]	5 - 10[c]
Benzoate, butyl *p*-hydroxy	Decision postponed	
Benzoate, ethyl *p*-hydroxy Benzoate, methyl *p*-hydroxy Benzoate, propyl *p*-hydroxy	0 - 2[d]	2 - 7[d]
Butylated hydroxyanisole Butylated hydroxytoluene	0 - 0.5[e]	0.5 - 2[e]
EDTA, calcium disodium	0 - 1.25	1.25 - 2.5
Isopropyl citrate mixture	0 - 7	7 - 20

[a]Source: FAO Nutrition Meeting *(34)*.

[b]The first part of the overall acceptable daily intake zone is termed unconditional, and this represents levels which can be safely used without further expert supervision and advice. The second part is termed conditional and represents levels of use that can be safely employed but at which it is thought desirable that some degree of expert supervision and advice should be readily available.

[c]As sum of benzoic acid and sodium and potassium benzoate (calculated as benzoic acid).

[d]As sum of methyl, ethyl, and propyl esters of *p*-hydroxybenzoic acid.

[e]As sum of butylated hydroxytoluene and butylated hydroxyanisole.

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